

A complex network diagram with various sized nodes (black, blue, grey) connected by thin grey lines. Some nodes are highlighted with larger circles. The background is white with faint grey circles.

# MS DMTs — BEYOND THE BASICS

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# DISCLOSURES

**Dr. Antonovich has no financial or non-financial interest to disclose.**

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# LEARNING OBJECTIVES

Upon completion of this activity, participants should be better able to:



EVALUATE NEW EVIDENCE FOR  
STARTING, SWITCHING, AND  
STOPPING DMT



ACCESS NEW INFORMATION ON DMT IN ORDER TO  
INITIATE AND SUSTAIN THE MOST APPROPRIATE  
TREATMENT FOR EACH PATIENT

# STARTING, SWITCHING, AND STOPPING DMT



# STARTING DMT — ESCALATION OR EARLY INTENSIVE?

- American Academy of Neurology (AAN) guidelines tell us it depends on severity of disease at presentation
  - “Highly active” disease should consider fingolimod, natalizumab, or alemtuzumab
- Harding, et al. put this to the test, except they classified DMTs a little differently
  - “Moderate efficacy” DMTs were identified as interferons, glatiramer, dimethyl fumarate, fingolimod, and teriflunomide
  - “High efficacy” DMTs were identified as natalizumab and alemtuzumab
  - Open label cohort
  - Primary outcome was 5 year change in Expanded Disability Status Scale (EDSS) score
  - Secondary outcome was time to sustained accumulation of disability (SAD) - these increases needed to be seen for at least 6 months:
    - EDSS increase by 1.5 if baseline 0
    - EDSS increase by 1 if baseline 1-5.5
    - EDSS increase by 0.5 if baseline 5.5 or higher



# EARLY INTENSIVE WINS!

- Early Intensive group had an average increase of 0.3 on EDSS and time to SAD of 6 years
- Escalation group had an average increase of 1.2 on EDSS and time to SAD of 3.1 years
- To make matters even more interesting, patients that were switched from a “moderate” efficacy to a “high” efficacy DMT within the 5 years had an average time to SAD of 3.3 years

SAD = time to sustained accumulation of disability

# OR DOES IT?

- ADRs

- Early Intensive group
  - 87% infusion related events
  - 47% developed an autoimmune condition
- Escalation group
  - 1.4% adverse reactions



- Study limitations

- Average age was much higher in escalation group (38.5yo) vs early intensive group (34yo)
- Adherence was not addressed
- Open label, not randomized
- Time period (starting in 1999) may include a wide variety of unique cases that may not be treated the same today

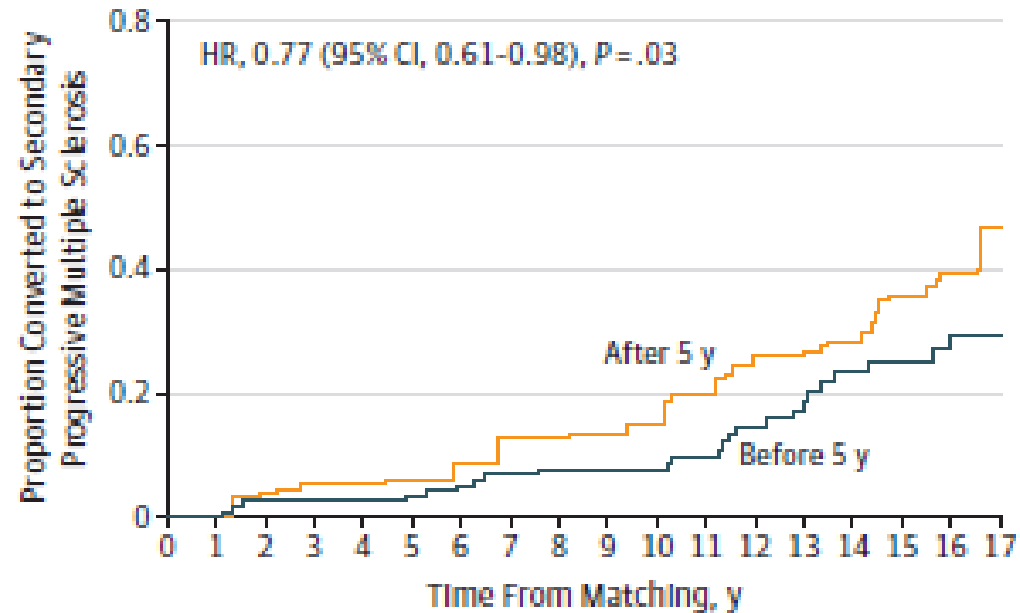
# STARTING DMT — WINDOW OF OPPORTUNITY

- Study utilizing data from *MSBase* — an observational cohort across 29 countries
- Looked at associations of DMT and conversion to secondary progressive MS
  - Time DMT was started
  - What DMT was started
  - If DMT was switched
- Each treatment group was matched to its own untreated group with similar average baseline characteristics for comparison
- Progression to SPMS was defined as:
  - 1 point increase on EDSS if baseline was 5.5 or less
  - 0.5 point increase on EDSS if baseline was greater than 5.5
  - Increases needed to be in the absence of relapse, confirmed at next appointment (at least 3 months later), and resultant EDSS had to be 4 or more



# EARLIER START, LESS SPMS

**A** Treatment with glatiramer acetate or interferon beta  $\leq 5$  y vs  $>5$  y of onset



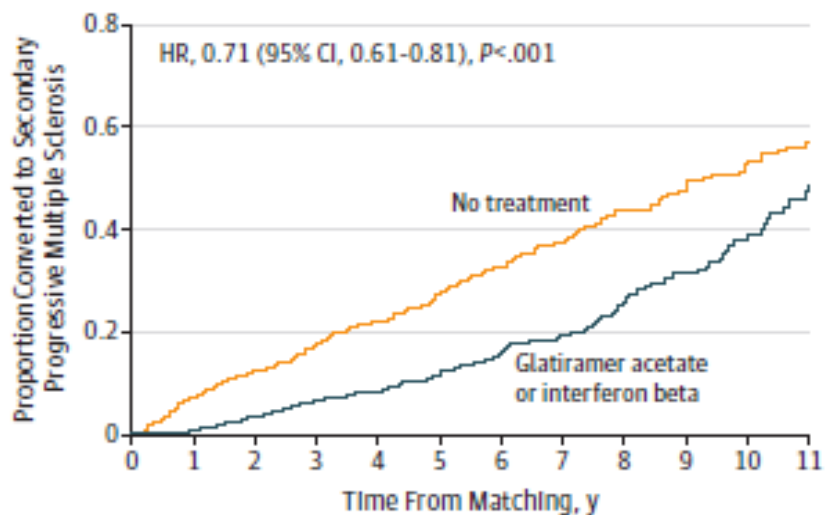
No. with follow-up data

Glatiramer acetate or interferon beta

$>5$ y	38	38	38	38	36	31	23	15	11
$\leq 5$ y	120	120	120	119	115	102	77	60	44

# COMPARING STARTING TIMES

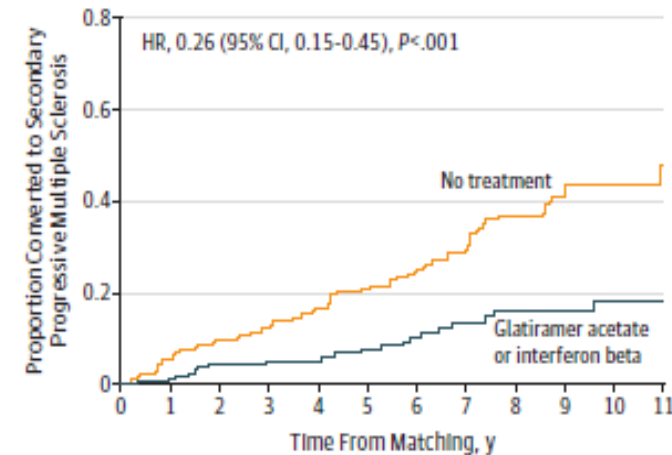
**A** Glatiramer acetate or Interferon beta vs no treatment



No. with follow-up data

No treatment	213	213	213	213	213	180	153	126	96	74	51	33
Glatiramer acetate or interferon beta	407	407	407	407	407	355	300	251	191	142	98	62

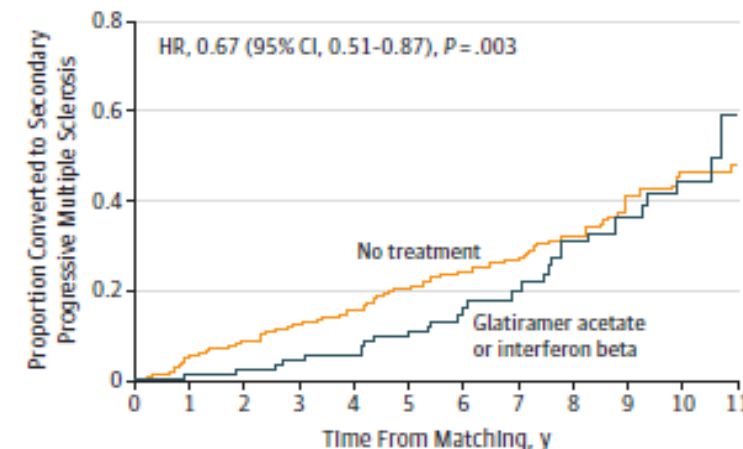
**B** Treatment with glatiramer acetate or Interferon beta within 5 y vs no treatment



No. with follow-up data

No treatment	104	104	104	104	104	88	74	60	51	39	27	20
Glatiramer acetate or interferon beta	164	164	164	164	164	144	116	93	78	61	43	28

**C** Treatment with glatiramer acetate or Interferon beta between 5 y and 10 y vs no treatment

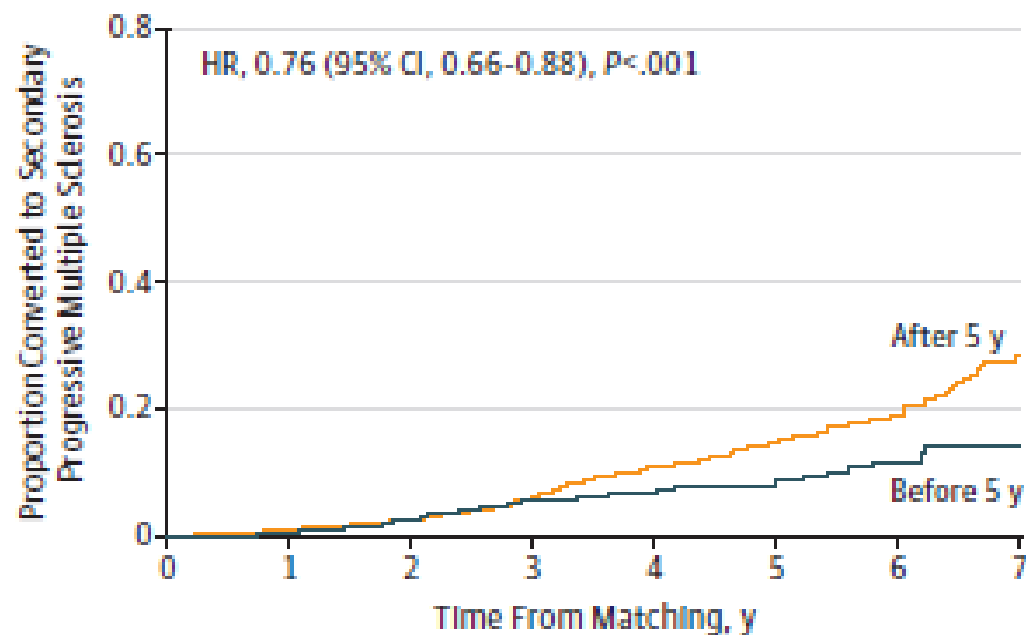


No. with follow-up data

No treatment	158	158	158	158	158	128	108	86	66	50	34	25
Glatiramer acetate	95	95	95	95	95	83	69	53	44	32	20	15

# WHEN TO ESCALATE THERAPY

**D** Escalation from glatiramer acetate or Interferon beta treatment to fingolimod, alemtuzumab, or natalizumab treatment  $\leq 5$  y vs  $>5$  y of onset



No. with follow-up data

Escalation to fingolimod, alemtuzumab, or natalizumab

$>5$ y after onset	331	331	331	331	331	204	106	49
$\leq 5$ y after onset	307	307	307	307	307	191	97	47

# CONCLUSIONS

- Secondary progressive MS can be prevented by:
  - Beginning treatment within the first 5 years of symptom onset
  - Switching to a higher efficacy DMT early as possible, if needed
- Strengths and Limitations
  - This started out as a huge study, but once each group was broken down, the actual size of each group was quite small
  - They attempted to do so many comparisons, some information seems to lack for completeness (data from timing of initiation of DMTs other than interferons and glatiramer was not collected)



# MORE DATA COMING SOON...

**Determining the Effectiveness of early Intensive Versus Escalation Approaches for RRMS (DELIVER-MS)**

ClinicalTrials.gov Identifier: NCT03535298

**Traditional Versus Early Aggressive Therapy for Multiple Sclerosis Trial (TREAT-MS)**

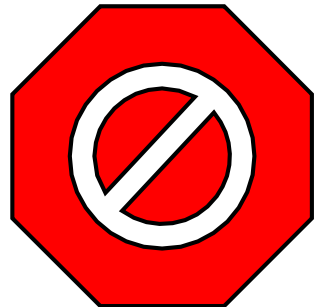
ClinicalTrials.gov Identifier: NCT03500328

# SWITCHING DMT

- Natalizumab to alemtuzumab – ANSWERS MS study
  - Average washout period was 115 days
  - Shorter washout led to lower relapse rate (less than 3 months was 0.36, 3-6 month 0.5, and 6-9month 1.9)
  - 3 out of 79 patients enrolled experienced serious infection, 8 had more minor infections
- Fingolimod to alemtuzumab
  - Average washout period was 2.7 months
  - Patients had normal lymphocyte count prior to initiating alemtuzumab
- Natalizumab to fingolimod or alemtuzumab - Pfeuffer, et al.
  - To fingolimod washout – 63 days
    - 5% had 1st dose bradycardia
    - 77.3% event free survival in the first year
  - To alemtuzumab washout - 91 days
    - 44.2% had 1<sup>st</sup> dose infusion reaction
    - 90.7% event free survival in the first year
  - All in all favored switch to alemtuzumab in regards to sequelae of potential cumulative immunosuppression

# DISCONTINUING DMT — CAN AGE GIVE US PEACE OF MIND?

- Retrospective observational study in people over 60 years old and had been on DMT for at least 2 years
- Of 600 patients, 178 (29.7%) discontinued therapy in study period
- Only 1 case of relapse!
- 19 of the 178 (10.7%) reinitiated DMT
- Though 25ft walk time did worsen in both groups there was no significant difference between continuers and discontinuers
- Discontinuers had a better quality of life
- Also more to come - **Discontinuation of Disease Modifying Therapies (DMTs) in Multiple Sclerosis (MS) (DISCOMS)** ClinicalTrials.gov Identifier: NCT03073603
  - Looking at 55 and older, prospectively
  - Taking PPMS and SPMS, though DMTs included are indicated for RRMS



# NEW WARNINGS AND OFF LABEL USE OF EXISTING DMT





# MORE WARNINGS WITH ALEMTUZUMAB

- Last year the FDA issued a warning for ischemic and hemorrhagic stroke and cervicocephalic arterial dissection associated with alemtuzumab
- In early 2019, the European Medicines Agency (EMA) launched a review and placed temporary restrictions on the use of alemtuzumab
- In November 2019, the Committee for Medicinal Products for Human Use provided their comments. Final EMA decision should be coming soon.
  - EMA recommended alemtuzumab update labeling to include risk of autoimmune hepatitis, hemophagocytic lymphohistiocytosis, and severe neutropenia
  - Advises that initiation of alemtuzumab should only be in adults that have highly active disease who have experienced failure of at least 1 other DMT. Also it should be administered in a hospital that can treat these potential acute adverse events.
  - Recommend LFTs before and during treatment now
  - Recommends that alemtuzumab no longer be used in patients with certain heart, circulatory, or bleeding disorders or in patients who have autoimmune disorders other than MS.

# VITAMIN D TO PREVENT AUTOIMMUNE DISORDERS FROM ALEMTUZUMAB

- How?
  - Many autoimmune conditions and hematologic disorders have higher interleukin 6 and 17 levels.
  - Interleukin 21 tends to be higher particularly in immune mediated thrombocytopenia (ITP)
  - People with MS who develop autoimmune conditions secondary to alemtuzumab tend to have higher basal levels of IL-21
  - Vitamin D can decrease the amount of inflammatory cytokines (IL-1,6,8,12,17,21 and TNF) and increase the amount of anti-inflammatory cytokines (IL-10)
- Authors suggest that keeping a vitamin D serum level of 30-100 ng/mL may help prevent development of autoimmune conditions
- Article presents interesting theory of associations. No causations or actual clinical trial.

# NATALIZUMAB EXTENDED INTERVAL DOSING (EID)

- First proposed a few years ago
- Varied schedules have been utilized from minor extensions (Q4week and 3 days) to longer extensions (Q8weeks and 5 days)
- Studies showed that there was not much difference in efficacy for patients who received EID vs. those receiving standard interval dosing (SID)
- Clinicians have been trying EID hoping it may lead to less ADRs, particularly progressive multifocal leukoencephalopathy (PML)

**Table 2** Comparisons of SID and EID groups on MS activity variables

	SID	Total EID	EED	LED	VED	Within EID
Participants (n)	1080	894	246	269	379	
Number of MRIs	2.91 (2.36)	4.98* (4.14)	4.98* (4.98)	4.05* (2.90)	5.63* (4.18)	VED, >EED, LED
Patients with T2 lesions	161/946 =17%	75/653* =11%	18/234 =8%	28/255* =11%	57/360† =16%	VED>LED, EED
Scans with T2 lesions	193/2607 7.0%	122/4253* 2.9%	17/1103* 1.5%	28/1084* 2.6%	77/2066* 3.6%	
Patients with Gad lesions	64/1019 =6%	65/683† =10%	9/195 =5%	11/142† =8%	45/346* 13%	
Scans with Gad lesions	111/2521 4.4%	93/3666† 2.5%	14/1060† 1.3%	13/537 2.4%	66/2069† 3.1%	VED>LED
Patients with clinical relapse	247/1068 23%	157/883* 18%	53/241 22%	24/266* 9%	80/376 21%	VED, EED>LED
Total relapses (per group, per participant)	354 0.35 (0.81)	218* 0.26 (0.70)	82* 0.41 (0.99)	46 0.13 (0.51)	90† 0.26 (0.57)	LED<EED, VED
Patients with steroids	218/960 23%	126/622 20%	42/203* 11%	25/148 17%	59/271 22%	LED, VED>EED
Total steroids (per group, per participant)	354 0.37 (0.87)	218 0.35 (0.93)	82* 0.40 (1.0)	46* 0.31 (1.0)	90 0.33 (0.78)	EED>LED
Adjusted annualised relapse rate	0.15	0.12*	0.11	0.08†	0.12	EED>LED, VED

Means and SDs (in parentheses).

(A) Comparisons in columns 2–5 are to SID group. Comparisons between the three EID groups (EED vs LED vs VED) are displayed in column 6. (B) Since the adjusted annualised relapse rate was allowed to vary across site, the rates in table 1 are the marginal means treating site as balanced.

\*Indicates EID group differs from SID group at  $p<0.05$ .

†Indicates EID group differs from SID group at  $0.05<p<0.10$ .

EED, early extended dosing; EID, extended interval dosing; LED, late extended dosing; SID, standard interval dosing; VED, variable extended dosing.

# EXTENDED DOSING DOES NOT ELIMINATE PML

- Italy publishes case series on patients receiving EID of natalizumab
  - By May 2018, 56 cases of PML were reported in Italy
    - 5 of these patients were treated with EID
    - 4 of the 5 were described in the case series. 5<sup>th</sup> not included due to incomplete data
  - Cases were all or mostly asymptomatic, often negative JCV in CSF, and initial imaging indicated small singular lesion for months
  - This kind of presentation is not unheard of in SID of natalizumab, but is much more rare
  - All four cases had increase in EDSS from PML diagnosis to final follow up of 1 point or less
    - With SID much larger increases are reported

# WHY EID MAY HAVE A MORE INSIDIOUS PML PRESENTATION

- Recent kinetics studies show the EID produces significantly less impact
  - Mean trough concentration of natalizumab
    - SID: 35.7 ug/mL
    - EID: 18.2 ug/mL
  - Alpha 4- integrin receptor occupancy
    - SID: 87.4%
    - EID: 78.2%

# PUTTING IT TOGETHER...



So, if EID of natalizumab can produce similar efficacy to SID plus, slow the progression of early PML and increase opportunity to diagnose it at an earlier stage with less lasting clinical effects, wouldn't we want to adopt this?



# IN THE PIPELINE

**A Study to Evaluate Efficacy, Safety, and Tolerability of 6-Week Extended Interval Dosing of Natalizumab (BG00002) in Participants With Relapsing-Remitting Multiple Sclerosis (RRMS) Switching From Treatment With 4-Week Natalizumab Standard Interval Dosing (SID) in Relation to Continued SID Treatment**

ClinicalTrials.gov Identifier: NCT03689972



# THE INDIVIDUALIZED DMT CONCEPT. WHERE ARE WE GOING?



# THAT “AGE”-OLD QUESTION: IMMUNOSENESCENCE

## Meta-analysis of age-dependent efficacy of DMTs

- A pool of DMT trials
- Attempts to answer the question: At what age does DMT stop working?
- Robust! – over 28,000 subjects
- All DMTs except cladribine were represented
  - Including drugs used for progressive MS – ocrelizumab, rituximab, siponimod

# AGE IMPACTS DMT EFFICACY

- The regression model predicts zero efficacy of DMT after age 53
- “High efficacy” DMT only outperforms “low efficacy” DMT for patients younger than 40.5 years old
- What could this mean?
  - Additional evidence against lifelong DMT use, but this indicates a younger age than we may have considered
  - Immunomodulating DMTs (antiCD20abs, cladribine, alemtuzumab) less effective in older people
  - Is a “deescalating” approach to DMT a possibility to consider more?

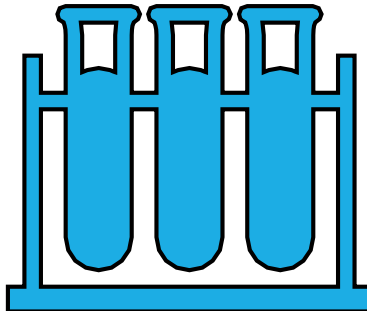
# BIOMARKERS

## Biomarkers accessible to most

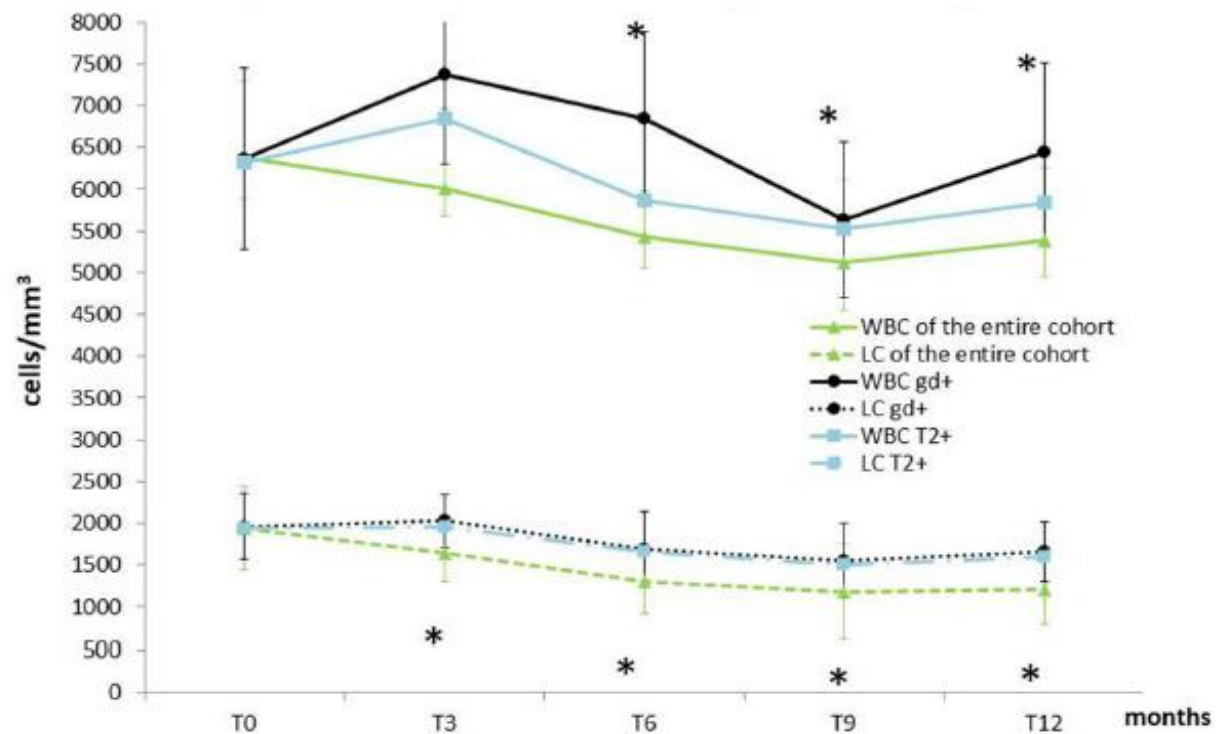
- White blood cell (WBC) count
- Lymphocyte count

## Biomarkers less accessible in clinics

- Neurofilament light chains
- Glial fibrillary acidic protein
- Soluble neural cell adhesion molecule



# PREDICTORS OF DIMETHYL FUMARATE RESPONSE



**FIGURE 2 |** Temporal profile of WBC and LC of the entire cohort compared with patients showing MRI activity at T12. Data are presented as mean  $\pm$  SD. WBC, white blood cell; LC, lymphocyte count; MRI, Magnetic Resonance Imaging; Gd+, Gadolinium enhancing; T2+, new hyperintense lesions; T0, baseline; T3, 3 months follow-up; T6, 6 months follow-up; T9, 9 months follow-up; T12, one year follow-up. \*Indicates Wilcoxon matched pair test  $P < 0.05$  (vs. T0) in the entire sample size.

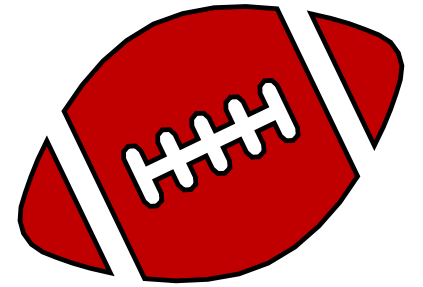
# CLADRIBINE BIOMARKERS IN THE PIPELINE

**Cladribine Tablets: Collaborative Study to Evaluate Impact On Central Nervous System Biomarkers in Multiple Sclerosis (CLOCK-MS)**

ClinicalTrials.gov Identifier: NCT03963375

MSBase Study:

**Cladribine: a multi-center Long-term efficacy Biomarker Australian Study (CLOBAS)**



# NEUROFILAMENT LIGHT CHAINS (NFL)

- Structural element that is released after axonal damage
  - PML
  - MS progression
- Dalla Costa et al. studied NfL serum concentrations in those not on DMT, on natalizumab without PML, on natalizumab with PML
  - NfL increases were seen in relapsing phases and PML
  - Either condition uniquely different levels of increase

# NEUROFILAMENT LIGHT CHAINS (NFL)

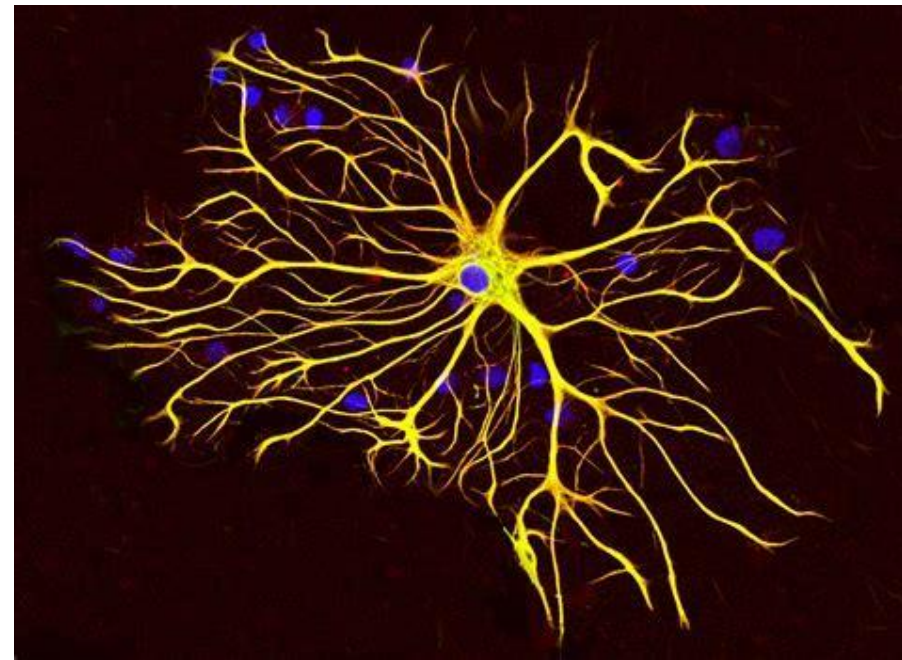
**TABLE. Baseline Characteristics of the Cohort of Patients**

Characteristic	MS Untreated Patients		NTZ Patients		PML Patients	
	Remitting Phase, n = 79	Relapsing Phase, n = 72 <sup>a</sup>	Remitting Phase, n = 125	Relapsing Phase, n = 11 <sup>a</sup>	Before Onset, n = 10 <sup>b</sup>	At Onset, n = 25
Serum NFL, pg/ml, median (IQR)	25.6 (12.1–43.0)	44.9 (16.4–64.1)	17.4 (8.2–27.8)	45.9 (40.8–51.8)	19.3 (13.7–21.5)	266.2 (63.5–354.2)

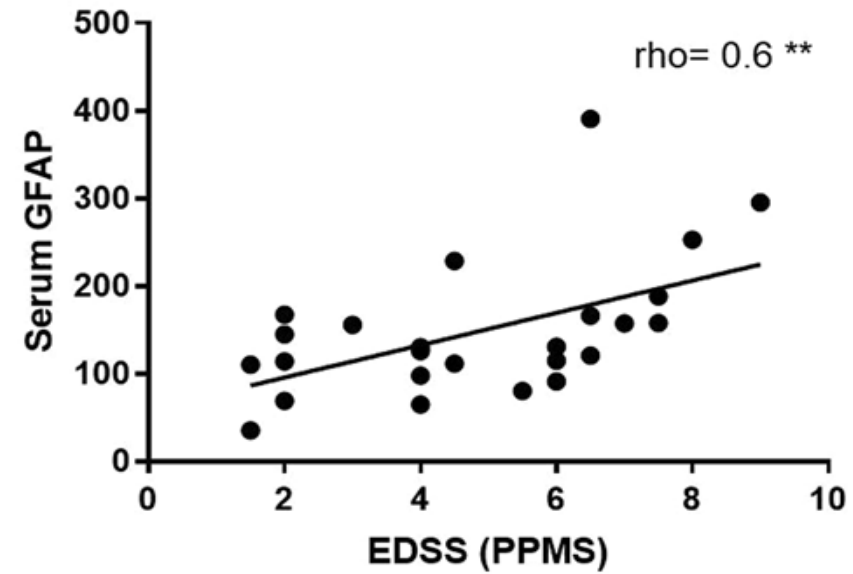
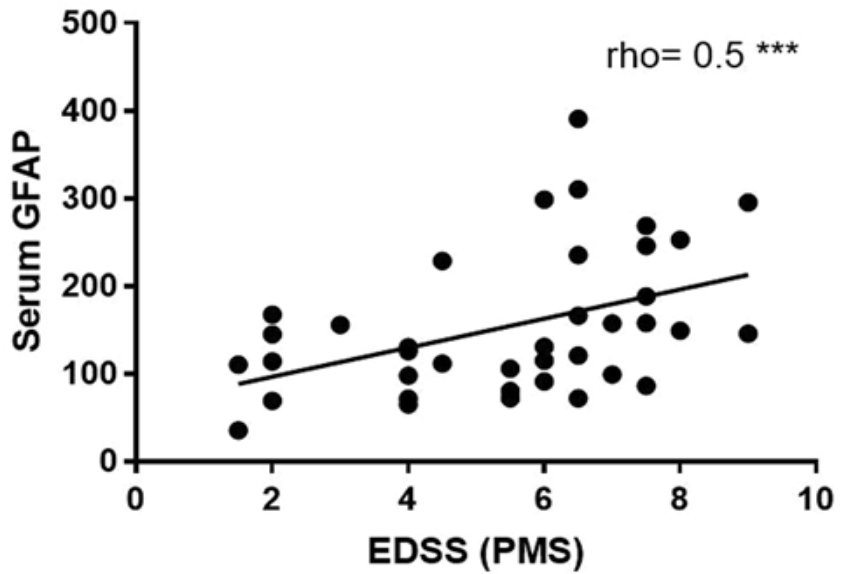


# GLIAL FIBRILLARY ACIDIC PROTEIN (GFAP)

- Indicator of astrogliosis
- Higher serum levels indicate higher lesion count – could this be MRI sparing or an interim monitoring level?
- Unfortunately, after correcting for age, almost all correlations lost statistical significance with regards to lesion count
- In progressive forms, serum GFAP correlated with EDSS even after correcting for age



# GLIAL FIBRILLARY ACIDIC PROTEIN – FIGURE 2



# NEURAL CELL ADHESION MOLECULE (NCAM)

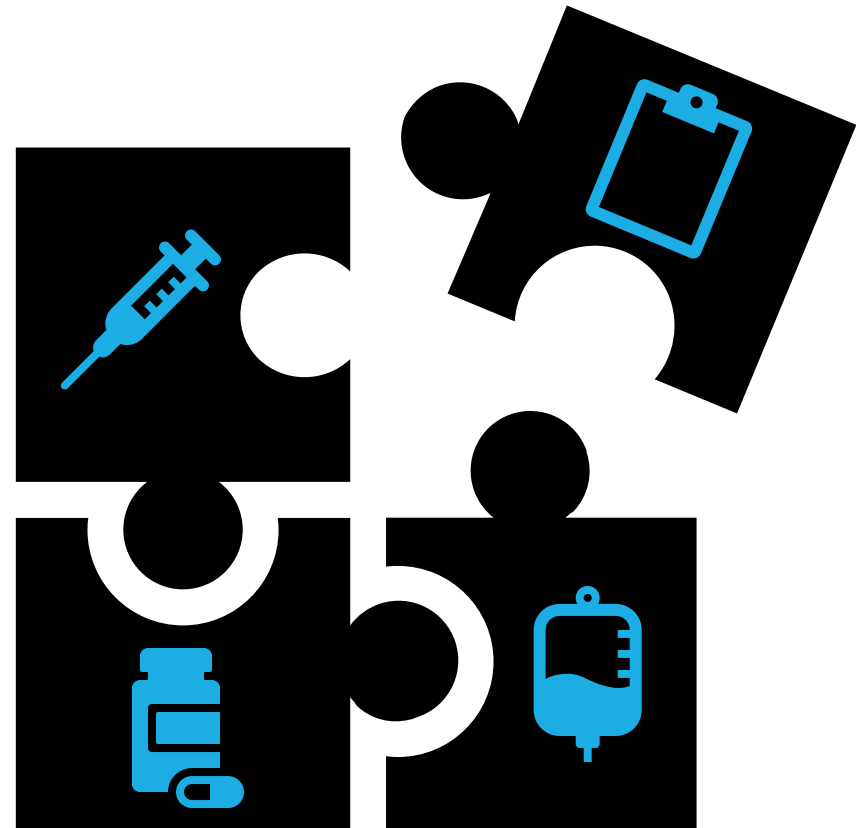
- Expressed in neurons and astrocytes in CNS
- Presence can suggest potential for regeneration and plasticity
- Soluble (sNCAM) form is found in CSF
- People with MS tend to have low sNCAM
  - PMS having less than CIS or RRMS
  - Further decreases are found after relapse
  - Steroids will increase level
- What does DMT do to sNCAM levels?

# NEURAL CELL ADHESION MOLECULE (NCAM)

- After 1 year (2 years for mitoxantrone) of therapy, average sNCAM changes:
  - Natalizumab +37.6 ng/mL
  - Mitoxantrone +61.8 ng/mL
  - Fingolimod -60.74
- Limitations:
  - 3 DMTs studied, only 2 are commonly used
  - Practicality would definitely limit use even if strong clinical correlations could be determined

# IN SUMMARY:

- Early initiation of DMT is key. What DMT to start is an individualized process.
- Incorporation of a discontinuing plan for DMT should be considered based on age and disease process.
- DMTs are an ever changing world. Be on the lookout for new evidence regarding dosing, safety, and efficacy.
- What's the “wave of the future” for MS treatment? Perhaps biomarkers that will objectively tell us if a DMT is working with less of the “watchful waiting” approach.



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